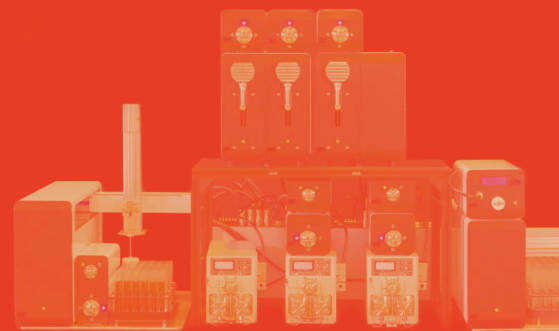
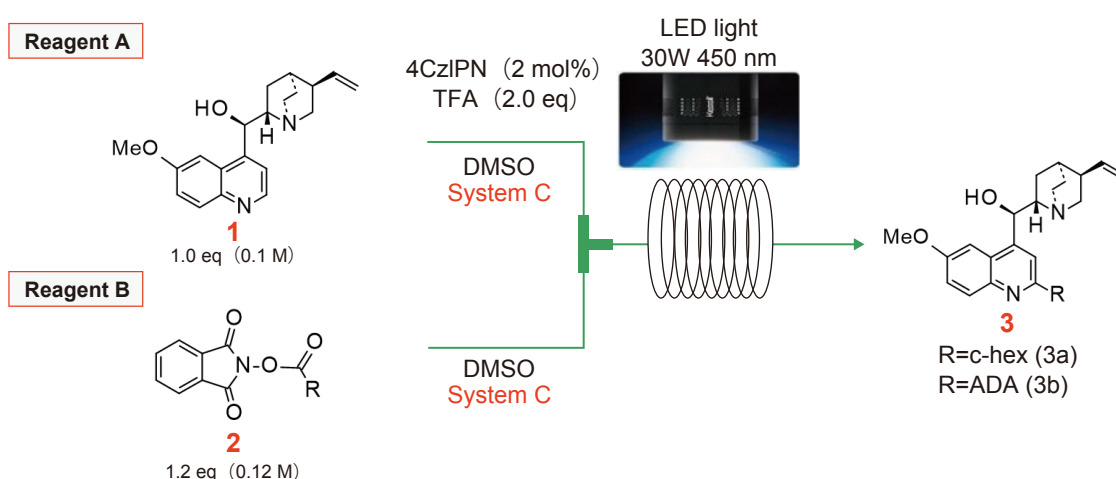


Photo Minisci reaction: 2-liquid mixture reaction



Overview

The basic 2-line system performs photoreactions in this application example. In addition to measuring and feeding optimum amounts of reagents, the **OptimFlow** enables reactions under LED lighting for photoreactions. The following illustrates an example of simplified library synthesis with the substrate and the catalyst for one reagent being premixed.



Preparation of Reagents

Reagent A: (-)-quinine **1** (64.9 mg, 0.20 mmol), 4CzIPN(2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile) (3.2 mg, 0.004 mmol) as a photocatalyst, and trifluoroacetic acid (30 μ L, 0.40 mmol) were dissolved in DMSO (2 mL) and received nitrogen gas injection for about 3 min.

Reagent B1: (1,3-dioxindolin-2-yl)cyclohexanecarboxylate **2a** (65.6 mg, 0.24 mmol) was dissolved in DMSO (2 mL) and received nitrogen gas injection for about 3 min.

Reagent B2: Similarly, (1,3-dioxindolin-2-yl)adamantane-1-carboxylate **2b** (78.1 mg, 0.24 mmol) was dissolved in DMSO (2 mL) and received nitrogen gas injection for about 3 min.

Device Setup

Line 1, System C ver.3.1; Line 2, System C ver.3.1
BPR = 0.5 MPa, the 2-reagent mode with a T-shaped mixer

Reactors

A bundle of PTFE tubes (each with an inner diameter of 0.5 mm, a length of 10 m, and a capacity of 1.98 mL) was placed in a PhotoRedOx Box (HepatoChem, Inc.) and set in the **OptimFlow**. The light source used was an LED lamp (30 W, 450 nm).

Fraction Collector

In each experiment, the reaction solutions were collected together in a test tube with the Pre Stream Ratio set to 20% and the Post Stream Ratio to 30%.

Experiment

The parameters for each experiment were set as shown in the software input example (Experimental parameter). The reaction times (Residence Time) were 10, 5, and 3 min, and the reference amount of Reagent A (Volume of Reagent 1) was 300 μ L. The concentration (0.10 M) of Reagent A after preparation was input into Conc. of Reagent 1 in Expts. 1 to 6. The concentration (0.12 M) of Reagent B1 was input into Conc. of Reagent 2 in Expts. 1 to 3, and the concentration (0.12 M) of Reagent B2 was input into Conc. of Reagent 2 in Expts. 4 to 6. Equivalent (1.00 and 1.20) of the reagents were respectively input into the Mol Ratio of Reagents 1 and 2.

For the Fraction collector, the Pre Stream Ratio was set to 20% and the Post Stream Ratio to 30%. To collect all reaction solutions in a test tube in each experiment, the Fraction Volume was set to 10000 μ L.

The flow rates, the amounts of reagents used, and the total amount of reaction solutions in the above settings can be viewed in the Calculated value tab.

Experimental parameter	Calculated value			Procedure & details						
	Expt.1	Expt.2	Expt.3	Expt.4	Expt.5	Expt.6	Expt.7	Expt.8	Expt.9	Expt.10
Reagent1	1A1	1A1	1A1	1A1	1A1	1A1	1A1	1A1	1A1	1A1
Reagent2	2A1	2A1	2A1	2A2	2A2	2A2	2A1	2A1	2A1	2A1
Reagent3										
Residence Time (min)	10.0000	5.0000	3.0000	10.0000	5.0000	3.0000	1.0000	1.0000	1.0000	1.0000
Volume Of Reagent1 (uL)	300	300	300	300	300	300	500	500	500	500
Conc of Reagent1 (M)	0.10	0.10	0.10	0.10	0.10	0.10	0.50	0.50	0.50	0.50
Conc of Reagent2 (M)	0.12	0.12	0.12	0.12	0.12	0.12	0.50	0.50	0.50	0.50
Conc of Reagent3 (M)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
MolRatio of Reagent1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
MolRatio of Reagent2	1.20	1.20	1.20	1.20	1.20	1.20	1.00	1.00	1.00	1.00
MolRatio of Reagent3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Pre Stream Ratio (%)	20	20	20	20	20	20	10	10	10	10
Post Stream Ratio (%)	30	30	30	30	30	30	30	30	30	30
Fraction Volume (uL)	10000	10000	10000	10000	10000	10000	1000	1000	1000	1000
Set BP1 (MPa)	0.5	0.5	0.5	0.5	0.5	0.5	0.1	0.1	0.1	0.1
Upper Limit of Pressure (MPa)	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50

Experimental Parameter

Experimental parameter	Calculated value			Procedure & details						
	Expt.1	Expt.2	Expt.3	Expt.4	Expt.5	Expt.6	Expt.7	Expt.8	Expt.9	Expt.10
Flow rate of PP-1 (mL/min)	0.099	0.198	0.330	0.099	0.198	0.330				
Flow rate of PP-2 (mL/min)	0.099	0.198	0.330	0.099	0.198	0.330				
Flow rate of PP-3 (mL/min)										
Flow rate of reactor1 (mL/min)	0.198	0.396	0.660	0.198	0.396	0.660				
Flow rate of reactor2 (mL/min)										
Volume of Reagent1 (uL)	300	300	300	300	300	300				
Volume of Reagent2 (uL)	300	300	300	300	300	300				
Volume of Reagent3 (uL)										
Main stream (uL)	600	600	600	600	600	600				
Pre stream (uL)	120	120	120	120	120	120				
Post stream (uL)	180	180	180	180	180	180				
Total collection Vol. (uL)	900	900	900	900	900	900				

Calculated value

After sequential reactions at room temperature, 5 μ L of each resulting reaction solution was diluted with 200 μ L of DMF and analyzed with a UHPLC-MS. The conversion ratio was calculated as the ratio to the product 3a or 3b and an unreacted raw material 1 using area normalization with the ELSD area value. From (1,3-dioxoisindolin-2-yl)cyclohexanecarboxylate 2a, (R)-(2-cyclohexyl-6-methoxy-4-quinolyl)-[(2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol 3a was obtained with the yields shown in the left table below. From (1,3-dioxoisindolin-2-yl)adamantane-1-carboxylate 2b, (R)-[2-(1-adamantyl)-6-methoxy-4-quinolyl]-[(2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol 3b was obtained with the yields shown in the right table below.

R=c-hex run	RT (min)	3a (%)	1 (%)	2a (%)	conv. (%)
1	10	63	28	8	69
2	5	41	36	20	53
3	3	25	45	28	36

R=ADA run	RT (min)	3b (%)	1 (%)	2b (%)	conv. (%)
1	10	85	11	-	89
2	5	78	14	5	86
3	3	53	17	27	76